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Cuijpers, W.J.M.J.; Smit, F.

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Review article

Subthreshold depression as a risk indicator for major depressive disorder: a systematic review of prospective studies

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Objective: In order to examine whether the incidence of major depressive disorder (MDD) is increased in subjects with subthreshold depression, or sD (clinically relevant depressive symptoms, without meeting criteria for a full-blown MDD), we conducted a review of prospective studies examining the incidence of MDD in subjects with sD.
Method: A systematic literature search was conducted. For all studies, the relative risk of developing MDD was calculated, based on person-years.
Results: Twenty studies (23 comparisons) were found, based on community samples, general medical patients and high-risk subjects. Most comparisons showed that subjects with sD had a consistently larger chance of developing MDD. The studies differed considerably in the definition of sD, the recency (occurrence of the last sD) and the in-/exclusion of lifetime MDD.
Conclusion: The incidence of MDD in subjects with sD is larger than in subjects without sD. Otherwise, the concept of sD is too broad to be used. In future studies, some consensus should be reached regarding the definition of sD.

P. Cuijpers[1,2], F. Smit[2]

[1]Department of Clinical Psychology, Vrije Universiteit, Amsterdam and [2]Trimbos Institute, Netherlands Institute of Mental Health and Addiction, Utrecht, The Netherlands

Key words: MeSH depressive disorder; incidence; review literature; prospective studies

Pim Cuijpers, Department of Clinical Psychology, Vrije Universiteit Amsterdam, Van der Boechorststraat 1, 1018 BT Amsterdam, The Netherlands.
E-mail: p.cuijpers@psy.vu.nl

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Introduction

Subthreshold depression (sD) has been found to be a highly prevalent condition (1, 2), with a considerable impact on the quality of life of patients (3–5), resulting in a strongly increased service utilization (6), and it has been found to be associated with large-scale economic costs because of disability days (7). A person can be considered to have sD when he or she has clinically relevant depressive symptoms, without meeting criteria for a full-blown major depressive disorder (MDD). The clinically relevant depressive symptoms in sD can either be operationalized as scoring above a cut-off score on a self-rating depression scale, as having a depressed mood with one or more additional symptoms of a mood disorder, or as meeting the criteria of minor depression (mD), as defined in the Appendix of the DSM-IV.

The sD can be considered as a significant risk-indicator of MDD because it can be regarded as a part of the prodomal phase of MDD (8). All or nearly all subjects who develop MDD can be assumed to have initially passed through a period (however, brief) of sD. On the contrary, not all subjects with sD will eventually develop MDD.

Assessing the incidence of MDD in patients exhibiting sD is important for several reasons. First, it is an important indicator for the clinical relevance of sD. Secondly, it is important for understanding the process by which an individual develops MDD and the role of depressive symptoms in the process. Thirdly, the increased risk is important because it may provide a rationale for the development of new interventions that prevent the onset of new cases of MDD. Several recent studies in this area have found evidence that it is indeed possible to reduce the number of new cases of MDD by intervening in subjects with sD (9–11).

Aims of the study

In this study, we conduct a systematic review of prospective studies examining the incidence of MDD in subjects with sD. We examine if the research in this area confirms the presupposition that subjects with sD have a greater probability of getting MDD than subjects without sD. We also examine how large the incidence rate is in sD, and whether the increased incidence rates are comparable for the differing studies.

Material and methods

Selection of studies

Studies were traced through several computerized literature databases (Medline, 1966–April 2002; Psychinfo, 1960–April 2002), by combining key words indicating sD (minor, subclinical), depression (MeSH and textword, depressi*) and the prospective character of the study (MeSH terms and textwords-like prospective, incidence, follow-up, epidemiology, cohort). In the computerized databases abstracts were read and papers which possibly met inclusion criteria were collected. Reference lists of retrieved papers were screened, and papers that possibly met inclusion criteria were retrieved and studied. Furthermore, references from major reviews in this area were examined (12–15).

In order to be included in the review, the study had to be prospective with at least two measurement points, and it had to include subjects meeting one of the definitions of sD. Furthermore, it was required that the presence of MDD was excluded at the first measurement by using a diagnostic interview [such as the Composite International Diagnostic Interview, CIDI (16) the Schedule for Clinical Assessment in Neuropsychiatry SCAN (17), or the Diagnostic Interview Schedule, DIS (18)], and it was required that a comparison group of subjects without sD and without MDD at the first measurement point was included. We did not include studies of patient groups who were treated for mental problems, as we assumed that the treatment would influence the incidence rates. sD could be defined as either meeting criteria for mD (as defined in the DSM-IV, the ICD-10 or the Research Diagnostic Criteria), having mood problems, or scoring above a cut-off point on a self-rating depression inventory, but below the threshold of full-blown MDD. We also included studies examining brief recurrent depression as this can also be considered to be a subthreshold condition for MDD (19).

Analyses

Follow-up period. Because the follow-up period of the studies differed considerably, we based the calculation of the incidence rates on person-years. That is, we divided the number of new MMD cases that occurred in the time period (the numerator) by the total amount of person-time units (person-years) of the group at risk (the denominator). Technically, this is known as the person-time incidence rate, or the incidence density rate. The person-time incidence rate is an appropriate measure of incidence when follow-up times are unequal (16).

Statistics. For each study we calculated the incidence rate ratio (IRR) which has the same interpretation as the more commonly known relative risk (RR), or its approximate, the odds ratio (OR).

Results

Included studies

A total of 43 198 subjects were examined in the 20 studies that met inclusion criteria, including 6049 subjects with sD. In three studies, two categories of sD with different definitions were examined (1, 20, 21). Therefore, the total number of comparisons between a group of subjects with sD with a control group was 23.

Three groups of studies could be distinguished (one study consisted of two separate samples that were categorized into two of the three following groups of studies): (i) studies examining community samples (10 studies with 13 samples, and with a total of 41 041subjects, including 5573 subjects with sD) (1, 2, 7, 8, 19, 20, 22–25, 28); (ii) studies of general medical patients (seven studies with seven samples; 1067 subjects, 268 with sD) (6, 26–31); (iii) studies of high-risk groups (three studies with three samples; 1090 subjects, 208 with sD) (28, 32, 33). Selected characteristics of these three groups of studies are presented in Table 1.

The studies differed on several characteristics, including the operationalization of sD, the length of the follow-up period, the composition of the comparison group and the measures of MDD (Table 1).

Overall outcomes

The RRs are reported in Table 2 for each of the comparisons in the studies. In 16 of the 23 comparisons a significantly increased RR of developing MDD was found for subjects with sD (11 of 13

Table 1. Prospective studies examining the incidence of major depressive disorder in subjects with subthreshold depression compared with the incidence in subjects without subthreshold depression

Study	Definition of sD	Rec sD	Ex LT	MDD measure	Population	Comparison group	Country	FU	N_{sD}	N_{ctr}	IR	Pr lost
Community studies												
Angst (19)	1–4 symptoms of depression or RBD	Nr	Nr	SPIKE	Community (18–19 years), 2/3 high SCL	No MDD, dysthymia	Switzerland	15 year	110	267	Nr	Nr
Broadhead (7)	Depressed mood and/or anh, with or without symptoms	6 month	–	DIS	Community (ECA)	No lifetime MDD, no past MDD	USA	1 year	176	1997	0.79	0.17
Bruce (22)	Lifetime history of depressed mood + 1–3 symptoms	Lifetime	+	DIS	Community (ECA)	No lifetime MDD	USA	1 year	514	2656	0.77	0.27
Chen (23)	Depressed mood and/or anh, total number of symptoms: 3	Lifetime	+	DIS	Community (ECA)	No lifetime MDD; no dysthymia	USA	13 year	136	1613	Nr	0.45
Cuijpers (2)	Depressed mood and/or anh, total number of symptoms: 2–4	12 months	+	CIDI	Community	No lifetime MDD; no key symptom	Netherlands	2 years	429	2838	0.70	0.15
Eaton (8)	Depressed mood + 2 or more symptoms	12 months	+	DIS	Community (ECA)	No lifetime MDD	USA	1 year	144	9959	Nr	Nr
Gotlib (24)	1 SD above mean on CES-D	Current	–	K-SADS	Adolescents from nine senior high schools	No MDD, CES-D below 1 SD above mean	USA	14 months	283	1382	Nr	0.12
Horwarth (1)	Two symptoms lifetime before T_0	Lifetime	+	DIS	Community (ECA)	No lifetime MDD	USA	1 year	2376	7524	Nr	0.27
	One key symptom only		+	CIDI	Community	No lifetime MDD; no key symptom	Netherlands	2 years	198	2838	0.70	0.15
Judd (20)	Minor depression (DSM-IV)	1 month	–	DIS	Community (ECA)	No MDD, dysthymia	USA	1 year	113	6238	Nr	Nr
	Two or more symptoms of MDD				Community (ECA)	No MDD, dysthymia	USA	1 year	350	6238	Nr	Nr
	One symptom of MDD				Community (ECA)	No MDD, dysthymia	USA	1 year	763	6238	Nr	Nr
Maier (21)	RBD and intermittent depression	Lifetime	+	SADS and DIGS	Community	No mood disorder	Germany	5 years	26	195	Nr	Nr
Oldehinkel (25)	Less than 5 MDD symptoms or distress	12 months	+	M-CIDI	Adolescents (14–17 years) community	No lifetime MDD; no dysthymia	Germany	20 months	65	1069	0.74	0.12
General medical patients												
Ballard (26)	RDC minor depression	Current	–	GMS/SADS/HAS+	Dementia patients	No RDC depression	UK	1 year	21	47	Nr	0.28
Maier (28)	Depressed mood and/or anh, total number of symptoms: 3/4	1 month	–	CIDI	GP patients, subset of larger population	No MDD, no RBD	Germany	1 year	23	193	–	–
Morris (29)	DSM-III dysthymia without duration criterion	Nr	–	CIDI	Hospitalized stroke patients	No MDD	Australia	15 months	14	29	Nr	0.43
Parmelee (30)	Depressed mood	Current	–	SADS/DSM-III-R	Elderly in residential homes	No current MDD	USA	1 year	74	319	0.64	0.48
Schleifer (31)	Minor depression (RDC)	Current	–	SADS/RDC	Myocardial infarction patients	No current MDD	USA	3 months	51	90	0.67	0.40
Wagner (6)	Depressed mood and/or anh and 2+ symptoms	6 months	–	DIS	GP patients	No MDD symptoms, CES-D < 15	USA	1 year	66	66	Nr	0.14
Starkstein (27)	Depressed mood and at least three symptoms	Current	–	PSE	Parkinson's disease	No MDD	USA	12 months	19	55	0.99	0.12
High-risk studies												
Brown (32)	Depressed mood + 1–3 symptoms	Current	–	PSE	Working class + single mothers	No MDD or anxiety disorder in last year	UK	1 year	25	215	0.91	0.23
Maier (21)	RBD and intermittant depression	Lifetime	+	SADS + DIGS	Relatives of depressed patients	No mood disorder	Germany	5 years	60	295	Nr	Nr
Warner (33)	Depressive symptoms	Current	+	SADS-C	Children (6–23) of depressed patients	No lifetime MDD	USA	2 year	13	105	Nr	0.79

Rec sD, recency of subthreshold depression; Excl LT, exclusion of lifetime major depressive disorder (+, yes; –, no); FU, follow-up period; N_{sD}, number of subjects with subthreshold depression; N_{ctr}, number of subjects in control group; IR, initial response; Pr Lost, proportion lost to follow-up; Anh, anhedonia; RBD, recurrent brief depression; nr, not reported; ECA, epidemiological catchment area studies; MDD, major depressive disorder; SCL, symptom checklist; DIS, diagnostic interview schedule; SADS, schedule of affective disorders; CIDI, Composite International Diagnostic Interview; RDC, research diagnostic criteria; SPIKE, Structured Psychopathological Interview and Rating of the Social Consequences for Epidemiology; K-SADS, Schedule for Affective Disorders and Schizophrenia for School-Age Children; DIGS, Diagnostic Interview for Genetic Studies; PSE, Present State Examination; GMS, Geriatric Mental State Schedule; HAS, History and Aetiology Schedule; RDC, Research Diagnostic Criteria; CES-D, Center for Epidemiological Studies, Depression Scale.

Table 2. Prospective studies of developing major depression in subjects with subthreshold depression: relative risks and incidence density rates

	LT MDD excl	Recency of sD	Study	Inc_{sD}	Inc_{ctr}	RR	95% CI
Community studies							
Minor depression	Yes	Past year	Eaton	0.083	0.015	5.72	1.54–14.97
			Cuijpers A	0.035	0.008	4.59	2.76–7.52
		Lifetime	Chen	0.015	0.003	5.91	3.48–9.76
			Bruce	0.020	0.017	1.15	0.52–2.31
	No	Current	Judd A	0.055	0.000	340.23	41.27–15651.82
One symptom only	Yes	Past year	Cuijpers B	0.018	0.008	2.36	0.90–5.30
	No	Current	Judd B + C	0.006	0.000	39.35	5.06–1774.27
At least one symptom	Yes	Lifetime	Horwarth	0.034	0.008	4.43	3.12–6.32
	No	Past year	Broadhead	0.108	0.011	9.73	4.92–19.00
Other definitions			Angst	0.023	0.013	1.81	1.11–2.90
			Gotlib	0.149	0.053	2.80	1.90–4.07
			Oldehinkel	0.122	0.030	4.09	1.99–7.77
			Maier 96B	0.049	0.008	5.91	2.49–14.16
Medical patients							
Minor depression	No	Current	Parmelee	0.176	0.058	3.04	1.34–6.67
			Wagner	0.220	0.000	3.41*	
			Schleifer	0.583	0.227	2.57	0.70–10.26
			Ballard	0.100	0.114	0.88	0.084–5.37
			Maier	0.190	0.037	5.14	1.10–20.23
			Starkstein	0.111	0.000	0.57*	
			Morris	0.063	0.118	0.53	0.010–5.37
High-risk groups							
Minor depression	Yes	Current	Warner	0.182	0.029	6.18	1.28–26.07
		Lifetime	Maier 96A	0.016	0.006	2.56	0.253–14.32
	No	Current	Brown	0.273	0.067	4.05	1.28–11.22

*No 95% confidence intervals reported because the incidence in the control group was zero.
LT MDD excl, lifetime MDD excluded yes/no; Inc_{sD}, incidence density rate in subjects with sD; Inc_{ctr}, incidence density rate in control subjects; RR, relative risk; sD, subthreshold depression.

comparisons from community studies; three of seven comparisons from medical patient studies; and two of three comparisons from the high-risk studies). Four of seven other comparisons also indicated an increased RR of developing MDD, although these did not reach significance levels. The three remaining comparisons did not indicate an increased RR, but none of the resulting RRs (indicating a decreased risk of developing MDD) was significant, and two of three examined subjects who for a large part had considerable cognitive dysfunction (26, 29).

Although the direction of the outcomes was confirmed by nearly all studies, the heterogeneity of the studies was very large. In the general population studies, the incidence density rates in subjects with sD ranged from 0.01 to 0.15 new cases per 100 person years, compared with 0.00–0.05 in subjects without sD. In general medical patients, the incidence density rates in subjects with sD ranged from 0.06–0.58 to 0.00–0.23 in subjects without sD. In the high-risk groups, the incidence density rates were 0.02–0.27 for subjects with sD, and 0.01–0.07 for subjects without sD.

The RRs in the general population studies varied from 1.15 to as much as 9.73 (in one study even much higher RRs were found, but these were based on very small samples and can be considered to be an outlier) (20). In the general medical patients, the RRs varied from 0.53 to 5.14 and in the high-risk groups from 2.56 to 6.18.

Operationalization of sD

Although considerable heterogeneity could be expected because of the differences in study designs, we examined potential sources of heterogeneity across studies. We found that especially the operationalizations of sD differed considerably in the 20 studies. We found that the differences mainly occurred along three important dimensions.

1. *Definition*: Four definitions of sD could be distinguished: (i) mD according to DSM-IV criteria, or a similar definition; (ii) mood problems with one other symptom, but not more; (iii) mood problems, with or without other symptoms; (iv) other definitions (e.g. a high score on a self-rating scale; and combinations of recurrent brief depression and other definitions of sD).
2. *Recency*: The period during which sD had been present before the first measurement varied. We distinguished three periods: (i) current; (ii) last year; (iii) lifetime. It was assumed that the prevalence of lifetime sD was

considerably larger than last year or current sD, but that the risk of getting MDD was larger in current sD.

3 *In-/exclusion of lifetime MDD*: As MDD is in many cases a recurrent or even chronic disorder, it was assumed that inclusion of lifetime MDD would result in a higher incidence rate of MDD for subjects with sD, reflecting the distinction between 'first-ever incidence' and 'repeat incidence' of MDD.

Using these three dimensions and the three groups of target populations, 72 ways (4*3*2*3) to operationalize sD were found to be possible. The 20 included studies covered 11 of these categories (Table 2). Only one of the categories consisted of more than two studies (current mD in general medical patients, no exclusion of lifetime MDD).

Further analyses

Given the considerable heterogeneity of included studies, a meta-analysis of the whole sample of studies was not feasible.

Discussion

We conducted a large review on a clinically important topic using rigorous inclusion and exclusion criteria. But this study also has several limitations. First, the number of studies examining the incidence of MDD in subjects with sD is relatively small, compared with the large variations in operationalizing sD. Apart from the differences in operationalization, several other differences existed between study designs, measurement instruments and populations. These large differences across studies made it impossible to conduct a meta-analysis. Another important limitation of this study is that we, because of the differences in follow-up periods, calculated the number of new cases over the total follow-up period, assuming that the new cases were evenly distributed over the follow-up period. This does not have to be the case, of course, and this could have distorted the outcomes. Because of these limitations, the results of this study should be considered with caution.

On the contrary, it is remarkable that in spite of the large amount of heterogeneity across studies, a fairly consistent pattern was found indicating a seriously increased incidence of MDD in sD compared to subjects without sD. Only very few studies did not support this conclusion. However, the studies included in this review do not allow us to determine exactly how much the incidence rate is increased by established sD. The heterogeneity of the set of studies is unsettling and the incidence rates differ dramatically between studies. The incidence rates probably depend heavily on the operationalization of sD. The varying definitions of sD, the differences in how long ago the sD was present in the subjects (current, last year, lifetime), the type and size of case and control samples, length of follow-up, and the in- or exclusion of subjects with a lifetime MDD, are probably very important characteristics of the studies, rendering them incomparable.

Because of the many definitions and operationalizations, the concept of sD is not useful in research or in practice. It can be safely assumed that the incidence of MDD in subjects with sD is larger than in subjects without sD, but how much of them will actually get MDD depends heavily on the definition.

It is crucial for future studies to reach some agreement on definitions and operationalizations of sD when examining the incidence of MDD in subjects with sD. From a clinical point of view, it would be most important to examine subjects with current sD, as these present themselves often in general or specialized general medical practices and can therefore be better identified than subjects with last-year or lifetime sD. Because mD has now been defined in the DSM-IV and a growing number of studies has used these criteria, it would be useful to apply this definition of sD in future studies.

The incidence rates of MDD in sD differed very much between studies. In general population studies, the incidence rates seemed to be smaller (not exceeding 0.15), while in general medical populations and in high-risk groups the incidence rates were higher (up to 0.58). Trials examining the effects of preventive interventions on the incidence of MDD in sD should concentrate on the general medical populations and the high-risk groups, as low incidence rates result in statistical power problems in preventive trials (34). This means that very large sample sizes are required to be able to show a reduction of this incidence rate.

It would be useful to improve the identification of subjects with sD who will develop MDD. One possibility for this would be to identity the presence of sD in subjects belonging to high-risk groups. For example, a recent study examining a preventive intervention focused on subjects who not only had sD, but also belonged to another high-risk group (adolescent children of depressed parents) (10). Such combinations of risk factors may well constitute the basis for a new generation

of preventive trials. Studies of these high-risk groups (and a corresponding high-incidence rate) need to include less subjects in order to get sufficient statistical power, and are therefore also of scientific interest (34).

The present review confirms that, although the concept of sD has to be defined more precisely, sD should be considered as a significant health problem, as it strongly predicts later onset of MDD. From this point of view, it is important to clarify and standardize the concept of sD, as was done with mD in the DSM-IV, and to continue developing preventive interventions aimed at the prevention of MDD and the treatment of clinically relevant forms of sD.

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